



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

Address: COMMISSIONER FOR PATENTS

P.O. Box 1450

Alexandria, Virginia 22313-1450

www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,746	09/09/2005	Navneet K. Ahluwalia	C1037.70035US01	2683
23628 7590 10/27/2009 WOLF GREENFIELD & SACKS, P.C. 600 ATLANTIC AVENUE BOSTON, MA 02210-2206				
EXAMINER				
LE, EMILY M				
ART UNIT		PAPER NUMBER		
1648				
MAIL DATE		DELIVERY MODE		
10/27/2009		PAPER		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/532,746

Applicant(s)

AHLUWALIA ET AL.

Examiner

EMILY M. LE

Art Unit

1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 July 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-14, 64, 65 and 72-79 is/are pending in the application.
- 4a) Of the above claim(s) 6 and 7 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5, 8-14, 64 and 72-79 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 07/29/2009 has been entered.

Status of Claims

2. Claims 15-63 and 66-71 are cancelled. Claims 76-79 are added. Claims 1-14, 64-65 and 72-79 are pending. Claims 6-7 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) a being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 1-5, 8-14, 64-65 and 72-79 are under examination.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. Claims 1-5, 8-14, 64 and 72-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Witherell et al.,¹ as evidenced by and in view of Hanecak et al.,² as evidenced by Kamal et al.³

In response to the rejection, Applicant argues that the combination of references do not render the claimed invention obvious. To support Applicant's position, Applicant argues that neither Witherell nor Haecak et al. nor Kamal et al. teaches that ISIS 6095, which has the CG motif stimulates the immune response. Applicant also argues that Witherell et al. can be interpreted as teaching away from the use of oligonucleotides that stimulate the immune response because he teaches that oligonucleotides that induce immune cell stimulation are problematic and that oligonucleotides that elicit less immune stimulation and complement activate are preferred. Regarding claims 64 and 77, Applicant notes that none of the references teaches ISIS-6095 has effects independent of antisense activity, as required by the claims.

Applicant's argument has been considered, however, it is not found persuasive. MPEP 2112(I) states, "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). In the instant case, while none of the references teaches that ISIS-6095 has immunostimulatory

¹ Witherell et al. ISIS-14803 ISIS Pharmaceuticals. *Current Opinion in Investigational Drugs*, 2001, Vol. 2, No. 11, 1523-1529.

² Hanecak et al. Antisense oligonucleotide inhibition of hepatitis C virus gene expression in transformed hepatocytes. *Journal of Virology*, August 1996, Vol. 70, No. 8, 5203-5212.

³ Kamal et al. Peginterferon alone or with ribavirin enhances HCV-specific CD4+ T-helper 1 responses in patients with chronic hepatitis C. *Gastroenterology*, October 05, 2002, Vol. 123, 1070-1083.

activity, however, such would have been inherent of the sequence itself for it comprises the required immunostimulatory motif/dinucleotides, CG. By having the required immunostimulatory motif, ISIS-6095 would necessarily be immunostimulatory. The mere absence of this teaching on the parts of the cited references does not render the references irrelevant because Applicant's discovery or appreciation of the immunostimulatory activity of oligonucleotides comprising CG motifs does not render the oligonucleotide patentable. The same discussion applies regarding the limitations cited in claims 64 and 77, which requires that the oligonucleotide acts independently of antisense activity. In the instant case, Applicant's discovery of another scientific explanation for the activity in which an oligonucleotide having CG motif also does not render the claimed invention patentable since such activity and its mechanism of action is inherent to the oligonucleotide. Regarding Applicant's assertion that Witherell et al. teaches away from the use of oligonucleotides that stimulates immune response, it should be noted that such is not found persuasive for Witherell et al. clearly suggests the use of ISIS-6095 in combination with ISIS-14803. Thus contrary to Applicant's assertion, Witherell et al. does not teach away from the use of ISIS-6095, which comprises the CG motif, with ISIS-14803.

As presented in the previous office action, the claims are directed to a process comprising the administration of a CpG immunostimulatory oligonucleotide comprising the sequence of 5'X₁X₂CGX₃X₄3', wherein X is any nucleotide and the oligonucleotide is 8-100 nucleotides long to a human subject having an HCV infection that was not successfully treated using previous non-CpG therapy. Claim 2, which depends on claim

1, specifies that the non-CpG therapy includes interferon-alpha. Claims 3-5, which depend on claim 2, specify that the non-CpG therapy includes interferon-alpha-2b, interferon-alpha-2a or consensus interferon-alpha; interferon-alpha and Ribavirin; and pegylated interferon-alpha and Ribavirin, respectively. Claim 8, which depends on claim 1, requires the oligonucleotide be a C class oligonucleotide. Claim 9, which depends on claim 1, requires the process to further comprise the step of administering interferon-alpha to the subject. Claim 10, which depends on claim 9, requires the interferon alpha be interferon-alpha-2b, interferon-alpha-2a or consensus interferon alpha. Claim 11, which depends on claim 9, requires that the interferon-alpha be administered substantially simultaneously with the oligonucleotide. Claim 12, which depends on claim 1, requires the oligonucleotide to comprise a backbone modification. Claim 13, which depends on claim 12, requires the backbone modification be a phosphorothioate backbone modification. Claim 14, which depends on claim 1, requires the oligonucleotide to comprise a semi-soft backbone. Claim 64 is directed to the process of claim 1 with the addition of the administration of an antiviral agent requiring that the activity is independent of antisense activity. Claim 72, which depends on claim 8, requires that the oligonucleotide comprise a semi-soft backbone. Claims 73-75, which depend on claim 64, requires that the antiviral agent be interferon-alpha, ribavirin, and that the antiviral agent be administered substantially simultaneously with the oligonucleotide, respectively. Claim 76, which depends on claim 64, requires that the oligonucleotide have a semi-soft backbone. Claim 77 is directed to the method of claim 1, requiring that the activity is independent of antisense activity. Claims 78-79, which

depends on claim 77, requires that the oligonucleotide be a C class immunostimulatory nucleic acid, and has a semi-soft backbone, respectively.

Witherell et al. teaches a process comprising the administration of ISIS-14803 to human subjects having an HCV infection that was not successfully treated using previous non-CpG therapy. The administration demonstrates that ISIS-14803 was effective in reducing HCV viral titer in said human subjects. Witherell et al. also discloses the use of ISIS-14803 as a single antiviral agent or in combination therapy with pegylated interferon and ribavirin in HCV infected subjects. [Clinical Development section, in particular.]

Witherell et al. also discloses while ISIS-14803 is effective in reducing HCV viral titer, it is unlikely that ISIS-14803 will be effective against HCV viruses. To overcome this limitation, Witherell et al. suggests the administration of ISIS-6095 with ISIS-14803. [Current Opinion section, in particular.] Witherell et al. notes that it is possible that the multiple inhibitory mechanisms activated by ISIS-14803 and ISIS-6095, it is possible that the combination of ISIS-14803 and ISIS-6095 would produce synergistic effects and delay the onset of resistance.

As evidenced by Hanecak et al., ISIS-6095 is a CpG containing oligonucleotide comprising the sequence of 5'X1X2CGX3X43', wherein X is any nucleotide and the oligonucleotide is 8-100 nucleotides long. ISIS-6095 comprises a phosphorothioate backbone modification.

In view of the suggestion made by Witherell et al., it would have been prima facie obvious for one of ordinary skill in the art to administer the CpG containing

oligonucleotide known as ISIS-6095 with ISIS-14803 alone or in combination of interferon and ribavirin. One of ordinary skill in the art, at the time the invention was made, would have been motivated to do so to reduce HCV viral titer in said HCV infected subjects. One of ordinary skill in the art, at the time the invention was made would have had a reasonable expectation of success for doing so because ISIS-6095 has proven to be effective at reducing HCV viral titer.

It is noted that Witherell et al. does not expressly suggest simultaneous or substantially simultaneous administration ISIS-6095 in combination with the other antiviral agents, including ISIS-14803, however, at the time the invention was made, it would have been prima facie obvious for one of ordinary skill in the art to adjust the administration protocol, including simultaneous administration. One of ordinary skill in the art, at the time the invention was made would have been motivated to do so to optimize the treatment. One of ordinary skill in the art, at the time the invention was made would have had a reasonable expectation of success for doing so because the determination of a workable or optimal administration protocol is routinely practiced in the art.

Regarding claims 14 and 72, while ISIS-6095 is an oligonucleotide that comprises a phosphorothioate backbone, it should be noted that Hanecak et al. discloses that the backbone is a result effective variable. Hanecak et al. teaches that modification of the backbone varies the reduction in HCV viral titer and nuclease resistance. Hence, at the time the invention was made, it would have been prima facie obvious for one of ordinary skill in the art to modify the backbone of ISIS-6095, including

the use semi-soft backbones. One of ordinary skill in the art, at the time the invention was made, would have been motivated to do so to vary the effectiveness of the HCV treatment and nuclease activity of the oligonucleotide. One of ordinary skill in the art, at the time the invention was made would have had a reasonable expectation of success for doing so because the use of various and modified backbones is routinely practiced in the art.

Additionally, while it is not readily apparent from the disclosure of Witherell et al. whether the combination therapy of ISIS 14803 with pegylated interferon encompasses ineteferon-alpha-2b. However, as evidenced by Kamal et al. pegylated interferon is also PEG interferon alpha-2a. [Abstract, in particular.]

Conclusion

5. No claims are allowed. Claim 65 is free of the prior art.
6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to EMILY M. LE whose telephone number is (571)272-0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/EMILY M LE/
Primary Examiner, Art Unit 1648

/E. M. L./